REMARKS/ARGUMENTS

The Examiner's attention to the present application is noted with appreciation.

Restriction Requirement. Applicant notes that the restriction requirement is made final.

Claims Rejection - 35 U.S.C. § 101. Claims 1 and 4-11 are rejected under 35 U.S.C. § 101 on the grounds that the claimed invention is not support by either a specific asserted utility or a well-established utility. Applicant respectfully traverses this rejection.

The invention of claims 1 and 4-11 provide a library with specific and defined characteristics to be utilized for metal ion complexation. As set forth in the "Field of the Invention", the invention provides a library "wherein at least a portion of each library constituent is conformationally constrained upon complexation with a metal ion." Page 1, lines 15-16. The library of claim 1 is a precursor to the metal ion complexed library. That is, the library of claim 1 includes the orthogonally protected sulfur atoms, prior to use of the library by removal of the protecting group and metal ion complexation. The utility of the library thus relates to "library constituents which are capable of binding a target molecule of interest, or mediating a biological activity of interest." Page 1, lines 18-19.

As taught in the specification, the libraries of the invention are distinguished and characterized in that they provide a "reverse turn" structure:

> In each of the methods and libraries provided, a specific conformational restriction is obtained upon complexing the peptides or amino acid sequences with a metal ion, such that the conformationally constrained peptide-metal ion complexes can serve as surrogates for reverse turn structures, such as beta turns and gamma turns commonly found in naturally occurring peptides and proteins.

Page 7, lines 24-28. This utility in part results in that a "specific conformational structure is obtained upon metal complexation." Page 7, lines 30-31. Because of use of different amino acid sequences within the library members, the libraries thus provide different and unique three-dimensional structures:

> Another object of this invention is to provide metallopeptide libraries, wherein the metallopeptides include a metal ion-binding domain and distinct, unique and different

> amino acid sequences, wherein the metallopeptides may be exposed to a substance to which one or more metallopeptides will exhibit specificity and affinity for the substance of interest.

Page 8, lines 7-10. Thus the libraries are characterized in that "they contain a reverse turn structure as a consequence of metal ion complexation." Page 8, lines 23-25. As further explained:

> Upon complexing the MBD [the metal ion-binding domain] with a metal, a specific structure results, forming a mimic of a reverse turn structure. The specific stereochemical features of this complex are due to the stereochemistry of the coordination sphere of the complexing metal ion. Thus the preferred geometry of the coordination sphere of the metal dictates and defines the nature and extent of conformational restriction.

Page 13, lines 9-13.

Thus the library members contain a "biological-binding domain" (abbreviated "BBD" in the specification) which is coextensive with all or a part of the sequence involved in metal ion complexation. Page 11, line 22 bridging page 12, line 19.

Based upon the specification and prior art of record, the utility of characteristic-specific combinatorial libraries is both disclosed and well-established. The Examiner states that the specification asserts the utility of the combinatorial library for "screening." (Office Action page 4, third paragraph) While "screening", in the sense of assays to determine biological activity or receptor specificity, is a procedure frequently employed with combinatorial libraries, the utility of combinatorial libraries is not for "screening" as such. Rather, the utility is to select and identify metallopeptides and metallo-constructs, which as disclosed by Applicant have a highly constrained structure, which bind to receptors of interest, and which may be accordingly selected. The application accordingly discloses use of libraries directed toward melanocortin receptors (Examples 6-9, page 26, line 13 and following); toward human neutrophil elastase (Examples 11-13, page 32, line 3 and following); and the like.

It is further submitted that the use and utility of combinatorial libraries is well known in the art; see the discussion and literature cited at page 1, line 21 through page 4, line 24. Further, Applicant notes that the Patent and Trademark Office has consistently recognized the inherent utility of combinatorial libraries *per se*, and has issued numerous patents wherein the claims are directly solely to combinatorial libraries. See, e.g., U.S. Patent Nos. 6,194,544, 6,025,371, 5,859,190, 5,824,483, 6,127,381 and 5,766,963. With respect to the Examiner's comment regarding "screening", it is noted that U.S. Patent No. 5,766,963 is drawn to a library "for biological screening".

Thus it is submitted that a specific utility is disclosed, that is, use of a library, and by extension a library precursor of claim 1, incorporating peptide elements comprising a site-specific reverse turn structure as a result of metal ion complexation, thereby mimicking the reverse turn structure found in the class of ligands characterized by a reverse turn structure. Stated differently, it is well-known in the biological arts that a number of peptides or proteins that bind to a receptor contain a reversed turn structure as the biologically active structure. Specific examples are given in the specification, including "various peptide hormones such as somatostatin, cholecystokinin, opioid peptides, melanotropins, luteinizing hormone releasing hormone, tachykinins and various antibody epitopes." Page 20, lines 18-20. The libraries and library precursors thus provide a set of compounds which are so designed as to mimic the reversed turn structures found in such known peptides or proteins.

There are numerous examples in the patent literature of libraries that are targeted to a specific epitope or receptor. No section 101 objection would be interposed to a library to a specific receptor, such as a melanocortin receptor, even though such a library would necessarily be used in "screening." Applicant's invention is not conceptually different; Applicant is not providing a "random" library in the sense of, e.g., completely random peptide sequences which, as a result of protein folding, will have random or unpredicted three-dimensional structures. Rather Applicant is providing a library with defined characteristics, in that the library members each, upon metal ion complexation, provide a reverse turn structure. This thus provides a specific utility, that is, a library of reverse turn structures.

Nor can it be doubted that a substantial utility is disclosed. Examples are given of libraries targeted for melanocortin receptors (Example 7) and human neutrophil elastase Examples 12 and 13), yielding through use of the libraries metallopeptide compounds with high affinity for the target.

Contained within the section 101 rejection is a section 112, first paragraph, rejection, asserting that "one skilled in the art clearly would not know how to use the claimed invention." This rejection is traversed for the foregoing reasons. It is further noted that the specific examples contained within the specification, such as libraries targeted for melanocortin receptors and human neutrophil elastase, provide ample instruction to one of skill in the art as to how to use the claimed invention.

Claims Rejection - 35 U.S.C. § 112. Claims 1 and 4-11 are rejected as containing subject matter not described in the specification, specifically relating to proviso "that the at least one amino acid residue containing at least one S protected by an orthogonal S-protecting group is not the terminal amino acid at either the N- or C-terminus." While Applicant has amended claim 1 to remove this language, Applicant maintains that the subject matter is described in the specification. See, e.g., the specification at pages 18-19, disclosing libraries wherein the amino acid residue containing a sulfur (depicted as "Ccc") is in the penultimate position. See also FIGS. 1A through 1J, including therein configurations wherein the cysteine or other amino acid residue containing a sulfur is not either the amino or carboxy terminus amino acid.

Claim Rejection - 35 U.S.C. § 112, Second Paragraph. The claims have been amended to, in part, address the concerns raised by the rejection. It is noted that "forming a metal ion-binding domain" characterizes the amino acid sequence; that is, the sequence can be bound to a metal ion as described in the specification. The remaining descriptions are not method steps, but rather characterize or describe, utilizing functional language, the library members.

Subsections (a) and (b) of claim 1 are each positive limitations on the "library". Claim 1 has been reformatted to make clear that the former subsection (a) provides a limitation as to each constituent library member while former subsection (b) provides a limitation as to the library.

The Examiner notes that "it is not clear whether the end product or component of the library containing the metal binding domain is solid bound." The library, as such, is claimed as library members

"solid bound" (i.e., "bound to solid phase"). The library members include the metal ion-binding domain. Thus the metal ion-binding domain is solid bound, albeit by means of a "cleavable bond."

The metes and bounds of "metal ion-binding domain" are, it is asserted, set forth in the specification. That is, it is the "amino acid ... sequence forming a ligand" with the metal ion. Page 11, lines 18-19. This is a defined in claim 1 as a minimum of two residues.

With respect to claim 4, this has been amended. It is submitted that the language "available for binding to a metal ion" with respect to the description of at least one nitrogen atom is functional language; i.e., it describes a nitrogen atom that may be bound to a metal ion, as opposed to a nitrogen atom which, because of its position within a structure, is not available for binding.

With respect to claims 8 and 9, the term "structural diversity" has been substituted with the corresponding term ("different selection or sequence of amino acid residues") now utilized in claim 1.

With respect to claim 11, this claim has been amended and new claim 23 added to address the objection.

Claim Rejection - 35 U.S.C. § 102. Claims 1 and 4-11 are rejected under 35 U.S.C. § 102(e) as anticipated by Sharma, U.S. 6,027,711. It is noted that Sharma is a named inventor on the instant application. Further, the owner of the '711 patent (shown on its face as "RhoMed Incorporated") is the owner of the instant application ("Palatin Technologies, Inc."), Palatin having acquired RhoMed. It is further noted that at least the current section 102(e) is not applicable, the '711 application not having published under section 122(b) (i.e., subsection 102(e)(1)), and the '711 patent not being "by another" (i.e., subsection 102(e)(2)).

It is important to appreciate that the heart of the invention resides in the discovery that an "orthogonal sulfur atom-protecting group" can be employed in solid phase chemistries. The phrase "orthogonal sulfur atom-protecting group" is discussed at length at page 14, line 20 bridging page 16, line 18. As discussed at page 14, starting at line 20, a free thiol is preferred for complexing with a metal ion. However, if peptide chains are synthesized on solid phase where the peptide chains include a cysteine or other amino acid with a free thiol, it is well known that the peptide chains can form a disulfide-linked

dimmer If mixed pool synthesis is employed, such that different sequence peptide chains bound to solid phase are included within the pool, then cross-linking of the disulfide bonds leads to a complex mixture of peptides or polymers unknown composition. The discovery that a category of sulfur-protecting groups exist that are both compatible with mixed pool peptide synthesis and metal complexation is critical to the invention. These protecting groups are called orthogonal sulfur atom-protecting groups. Ordinary protecting groups, such as S-Benzoyl and the like, are not compatible with peptide synthesis. Thus it was the discovery that protecting groups can be employed that are (a) compatible with methods of peptide synthesis and (b) can be deprotected in situ, so that the peptide chain can be complexed to a metal ion without cleaving the peptide chain from the solid phase resin. See page 14, line 35 bridging page 15, line 11.

The limitations of an "orthogonal sulfur atom-protecting group" are included in claim 1, by reason of the phrase defining the same as "compatible with peptide solid phase synthesis and removable without cleaving the peptide from the solid phase." Further, the phrase is adequately defined within the specification as set forth above.

The '711 patent does not disclose the use of an orthogonal sulfur atom-protecting group. Thus the '711 patent does not anticipate the instant invention.

Claim Rejection - 35 U.S.C. § 103. Claims 1 and 4-11 are rejected under section 103(a) as being unpatentable over Hnatowich et al. (U.S. 5,980,861). Applicant respectfully traverses the rejection.

Hnatowich et al. disclose a "library" of chelator compounds, as well as a library of chelator compounds bound to a nucleic acid, wherein the biological activity (binding to a target of interest) is a function of the nucleic acid. There is no claim or disclosure that the chelator compounds of Hnatowich et al. contribute to or form any part of the biologically active portion of the molecule.

Claim 1 is written to peptide sequences where at least one amino acid residue is outside the metal ion-binding domain. Thus claim 1 specifically includes, as a positive limitation, "a sequence of one or more amino acid residues at the N- or C-terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain." Thus in all embodiments of the combinatorial library claims

the sequences necessarily includes one or more amino acids which are not involved in complexation of a metal ion. Hnatowich et al. '861 discloses only "chelator compounds" in which each amino acid residue binds to the metal ion. See '861 at col. 10, line 67 bridging col. 12, line 54; see also col. 14, lines 15-41. In general, Hnatowich et al. teach only tri-peptide chelator sequences in which each amino acid of each tri-peptide is involved in complexation of a metal ion. Hnatowich et al. then covalently complex the chelator sequences to the disclosed biologically active sequences, such as the disclosed nucleic acids. This distinction is critical; in Applicant's invention conformationally constrained sequences (i.e., sequences constrained by complexation to a metal ion) are specific to a target of interest. In Hnatowich the only objective is discovery of the best chelate for a specific chelate application, such as with a nucleic acid. Thus there is no reason or teaching why, in Hnatowich et al., one or more additional amino acid residues would be placed on either side of the metal ion-binding domain. However, in Applicant's invention these additional amino acid residues contribute to and form an essential part of the structural diversity required for a combinatorial library of metallopeptides directed to ligands of interest.

Hnatowich et al. does not disclose or teach the orthogonal sulfur atom-protecting group as claimed in Applicant's invention. The specific "S-protecting" groups disclosed in Hnatowich et al. are not orthogonal sulfur atom-protecting groups meeting the definition and utility specified by Applicant. The S-acetyl protecting group disclosed by Hnatowich et al. (col. 14, line 36) is not an orthogonal protection group because, among other reasons, its use is not compatible with methods of peptide synthesis. An S-acetyl group, which is a thioester group, is unstable and therefore not usable during certain peptide synthesis steps. For example, removal of Fmoc groups from amino functions by piperidine would also hydrolyze a thioester bond. Use of conventional peptide synthesis reagents, such as piperidine, is specifically contemplated by Applicant (see, e.g., Example 1, page 24, lines 30 - 34), and it is a specific requirement of an orthogonal S-protecting group that it be compatible with methods of peptide chemistry (Specification, page 15, lines 1 - 4).

A copy of pages 298 and 299 from Protective Groups in Organic Synthesis, Theodora W. Green and Peter G.M. Wuts (Eds), Wiley & Sons, Inc., 1991, is attached. This reference establishes that it is known in the art that S-acetyl protecting groups are incompatible with conventional peptide synthesis.

In Hnatowich et al. it is specifically claimed that the method and compositions described therein are preferable to prior art methods, citing benzoyl MAG_3 as a specific S-protected chelate (col. 2, lines 14-54). Applicant also discusses the exact same chelate, and notes that it is not compatible with methods of peptide synthesis. (Specification, page 14, lines 29 - 34). The improvement sought and specifically discussed in Hnatowich et al. is that the S-acetyl groups, such as an N-hydroxysuccinimide derivative of acetyl-MAG_3, can be deprotected under "mild conditions" (col. 12, lines 19-35). However, this makes S-acetyl groups and the "mild conditions" S-protecting groups of Hnatowich et al. even less suitable for use in Applicant's invention than the prior art benzoyl MAG_3.

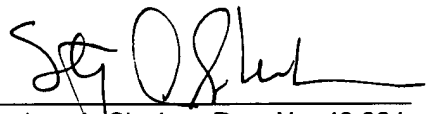
Claim 1 is further amended to provide that each library member "consists of " the defined amino acid sequences. This thus excludes the nucleic acid compositions covalently bound to a chelate as disclosed by Hnatowich.

In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, the Examiner is cordially invited to telephone the undersigned attorney for Applicant at the telephone number listed below.

Also being filed herewith is a Petition for Extension of Time to August 26, 2003, with the appropriate fee. Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

By: 

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